

It is believed that many interested parties in the Industry, Patent Practitioners, and even some EPO Examiners think that the Decision T 356/93 rejecting the Plant Genetic Systems NV patent was wrong. Another case relating to transgenic plants in which the same problem arises has now been rejected by the EPO Examining Division and is currently under Appeal.<sup>12</sup> Claim 19 of the patent application reads as follows:

A transgenic plant and the seed thereof comprising recombinant DNA sequences encoding

- (a) one or more lytic peptides, which is not lysozyme, in combination with;
- (b) one or more chitinases; and/or
- (c) one more  $\beta$ -1,3-glucanases

in a synergistically effective amount.

The grounds of appeal were filed by the Patent Attorney representing Novartis on 5 November 1996. In the Grounds of Appeal he said:

A given plant cannot be considered as a variety simply because it carries some additional gene(s) introduced by genetic engineering that cause(s) a distinct and stable genetic characteristic while the remainder of the genome can be nonhomogeneous and genetically unstable. A variety cannot be defined by a single new trait but only by substantially all of its traits in combination. Hence, a plant variety is always made up of an *individualized* (unique genome or a combination of unique genomes, but can never be characterized by a *generalized* genotype, on which the plants of pending claims 19 to 22 are based. As long as a claim does not require overall genetic homogeneity and stability, it simply does not solely encompass plant varieties. Furthermore, a plant produced by genetic engineering is not automatically a plant variety, even if the starting material applied was a plant variety.

None of pending claims 19 to 22 requires overall genetic homogeneity and stability of the transgenic plants addressed therein. Thus, none of these claims specifically relates to a 'plant variety' in the sense of Article 53(b) EPC.

The Appeal Board of the EPO is due to decide on the case at Oral Proceedings on 13 October 1997. If the Appeal is successful and the patent claims are granted it will re-establish the possibility for patenting genomically stably modified crops as such in Europe. If this result occurs, it will be in line with the current form of wording of the European Council and Parliament's proposal for a Directive on the Patentability of Biotechnological Inventions. The Directive clearly envisages the possibility of patenting a plant having a stable and transmissible genetic characteristic, because in the draft version of the Directive dated 25 June 1997 it is stated as follows.

The protection conferred by a patent on a process that enables a biological material to be produced possessing specific characteristics as a result of the invention shall extend to biological material directly obtained through that

process and to any other biological material derived from the biological material directly obtained through multiplication or propagation in an identical or divergent form and possessing those same characteristics.

Whereas this Directive shall be without prejudice to the exclusion of plant and animal varieties from patentability; whereas on the other hand inventions which concern plants or animals are in general patentable provided that the practicability of the invention is not technically confined to a single plant or animal variety ...

Whereas a plant totality which is characterized by a particular gene (and not its whole genome) is not covered by the protection of new varieties and is therefore not excluded from patentability even if it comprises plant varieties ...

The outcome of the Novartis Appeal case at the EPO will be of great interest and significance to those concerned with the opportunities for protecting molecular biological inventions relating to transgenic crops and crop protection.

## REFERENCES

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2. EP-B-0169672 Harvard Oncomouse; Appeal Decision T19/90 (1990).
3. EP-B-0112149 Howard Florey Institute; Human Relaxin Gene; Opposition (1991).
4. EP-B-0122791 Lubrizol; Plant Gene Expression (1989).
5. EP-B-0242236 Plant Genetic Systems NV; Herbicide Resistance; T356/93 (1995).
6. EP-B-0271988 Zeneca; Delayed Softening of Tomatoes (1995).
7. EP-B-0341885 Zeneca; Delayed Softening of Tomatoes (1995).
8. EP-B-0301749 Agracetus Inc; Transformed Soyabean Plants (1994).
9. EP-B-0044723 Lubrizol; Production of Hybrid Plants; Appeal Decision T320/87 (1988).
10. EP-B-0010588 Ciba-Geigy Oxime Treatment of Seeds, Appeal Decision T49/83 (1983).
11. Enlarged Board of Appeal Decision GP G03/95 (1995).
12. EP-A-0448511 Novartis; Transgenic plants that contain genes that are able to express lytic peptides and hydrolytic enzymes; Appeal (1996).

## Is This the End of Chemical Plant Protection?

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When new techniques and concepts allow progress to be made on problems that have long proved to be intractable to established methodologies, this can initially result in over-optimistic expectations of what the new techniques can achieve. The idea that transgenic crop plants could eventually eliminate pesticide use may

be an example of this. It will be argued that, although transgenic crops will certainly have a profound influence on agricultural practice, they cannot, for the foreseeable future, render chemical plant-protection obsolete or unnecessary, especially if the current, high levels of agricultural productivity are to be maintained and improved as world demographics demand that they must.

Herbicide-resistant crops are clearly not designed to eliminate pesticide use and thus, strictly speaking, fall outside the scope of the title of this article, but are included because they are intended to influence pesticide use quite substantially.

The first problem is one of communication, and its importance should not be underestimated. It will be very difficult to convince the public that crops resistant to total herbicides will be of any benefit to anyone except perhaps large-scale farmers and the agrochemical industry. There is a vociferous body of opinion that these crops and the products made from them are being forced upon the public without giving them any choice. This issue has been allowed to overshadow any potential benefits and should be addressed publicly if such crops are to be widely accepted. No matter what evidence is produced that the herbicides concerned are toxicologically safe and environmentally benign or that products derived from transgenic and non-transgenic crops are indistinguishable, some will argue that herbicide-resistant crops can lock agriculture even more firmly into what is frequently referred to as a vicious circle of pesticide use. Of course, this is a complete misunderstanding of the situation which, if those who so argue were faced with the prospect of hoeing a few million hectares of wheat, they might better appreciate, but there will always be a significant minority whose gene-technophobia renders them inaccessible to rational discussion. However, arguments in favour of these plants which would convince a sceptical, but relatively open-minded layman that there is a public benefit in cost or environment terms are currently lacking or have failed to reach the public domain.

In addition to this essentially public relations problem, there are factual issues which, to my mind, have not been sufficiently addressed in public. The first of these is the possibility of the transfer of herbicide-resistance genes to weeds. Laboratory experiments have been reported, but there are few hard data that I am aware of to show that it has or has not happened in the field. Of course, it is impossible to prove a negative and there may be understandable reluctance to publish positive results, but, if gene transfer has been documented, complete openness and the publication of strategies for dealing with it and with the related problem of volunteer crops can only have a positive influence on the press and public opinion in the long term.

Another possible problem is that not all weeds may be well controlled by the herbicides for which resistant

crops are available. The commercial introduction of any new cultivar could be regarded as the final trial in a series of field experiments, after which the new cultivars succeed or sink to oblivion according to their ability to find a niche in the market place. The same is true of herbicide-resistant transgenic crops. However, they are being rapidly introduced on an almost unprecedented scale. As such, they represent perhaps the largest field trial that has ever been conducted. The relevant total herbicides will be used on an enormous scale in situations where they have never been used before. The population dynamics of the treated fields are sure to be greatly altered by this new selection pressure. Currently obscure and economically unimportant plant species could become a problem if they are less susceptible to the total herbicides for which resistant transgenic crops are available. In such cases an additional spray with a selective herbicide would become necessary and thus affect the economics of the whole system.

Insecticides are mainly non-selective and, since the publication of Rachel Carson's *Silent Spring*, have attracted perhaps the most adverse publicity of all agrochemicals. Any technology which can reduce their use is clearly of great advantage to the user, the public and the environment and should be welcomed by even the most radical environmentalists. The benefits offered by plants genetically engineered to resist insect attack are so obvious and simple to communicate that they are likely to be an important factor in public acceptance of transgenic plant technology. Precisely because it is so difficult to find anything negative to say about them it is extremely important to be clear about their limitations. As already noted, no matter what the evidence, there are those who will be sceptical of even the most circumspect claims made for the benefits of transgenic crops and the slightest hint of overstatement would be enough to cast doubt on the credibility of the whole idea. For example, although transgenic cotton plants expressing the insecticidal protein from *Bacillus thuringiensis* (Bt), required fewer sprays for adequate pest control than conventional varieties, the need for spraying was not eliminated.

It should also be conceded that Bt transgenic crops do not offer a once-and-for-all solution. Spray applications of Bt have been in use for over 20 years and there are now several clear examples of resistance in field populations of lepidoptera, reaching as high as 1000-fold. Other orders of insects show natural intra- and interpopulation variations in susceptibility which could form the basis for the development of resistance of practical significance. There is no biological reason to believe that insect populations should have any greater difficulty in overcoming the challenges of transgenic plants than they have in overcoming the selective pressures of sprayed insecticides. The continuous, rather than intermittent, presence of the Bt toxin may even speed up the selection process, even if there is

a fitness penalty. Similarly, beneficial predators may starve or migrate, thus enhancing the survival and interbreeding chances of Bt-resistant individuals. In the worst scenario, the fact that Bt resistance genes have already been enriched in some species could accelerate the process still further when transgenic crops are introduced. As is usual in plant protection, it will be a matter of continuous development to keep pace with natural populations who can carry out more genetic crosses in one minute than the combined resources of the crop protection industry can hope to achieve in a decade. As with conventional insecticides, new toxins that can be engineered into plants will be continuously required for the long-term success of this strategy.

Conventional plant breeders have long been aware that breeding for resistance to fungal diseases is difficult, at best only partially successful, and the resistance is frequently fairly short-lived. Investigations into the molecular biology of this type of resistance have done more to illustrate why this is so than to offer simple solutions.

The front line of plant resistance to fungal attack is a surveillance system which perceives the presence of the fungi and initiates the defence response. The perceptive elements of the plants are encoded by resistance genes whose products detect the corresponding products of the fungal avirulence genes on a gene-for-gene basis. Of necessity, resistance genes are highly specific because large-scale, inappropriate triggering of the defences would be highly detrimental to the plant, particularly in the case of the hypersensitive response. This necessary specificity is the root of the problem for the production of transgenic plants with broad-spectrum resistance to fungal diseases. Wild plant races are relatively local in distribution and evolve in parallel with the local fungal population. The evolutionary arms race between the two tends toward equilibrium. Traditional agriculture based on saved seed did not completely interrupt this co-evolution as the farmers tended to save seed from the plant which thrived best under the local conditions. In contrast, the high-yielding varieties of the green revolution are planted over vast areas and encounter a wide range of pathogen races. The co-evolutionary relationship is broken and plants simply do not have the diversity of resistance genes to recognise all the races of pathogens they encounter. Modern agriculture cannot tolerate the reduced yield of crops in equilibrium with local pathogens and it is difficult to imagine how, even using modern techniques of gene manipulation, crops expressing the necessary wide range of resistance genes could be produced. Even if it were possible, fungi can respond quite rapidly to selective pressure of this type by performing immeasurably more genetic crosses than even a molecular biologist can hope to achieve. Consequently, unless it can exploit a radically new concept, transgenic plant technology can only supplement the efforts of traditional plant breeders as far as resistance to fungal diseases is concerned.

A problem of general relevance to the introduction of all transgenic crops is the question of varietal diversity. The relatively few high-yielding cultivars of most major crops currently in use have been introduced at the expense of thousands of locally adapted varieties. In the developed world, at least, this has also greatly contributed to a situation in which essential, basic foodstuffs are more plentiful and cheaper, relative to income, than they have ever been in history. Nevertheless, three related negative consequences are frequently cited, the first of which is the loss of genetic diversity itself. In this context it is relevant to ask whether the currently low levels of diversity will be reduced still further by the introduction of transgenic crops. Any such loss is irreversible and must be avoided; seed banks should not be allowed to become seed graveyards. Secondly, high-yielding varieties are not adapted to local environmental conditions and usually require higher levels of fertiliser and irrigation in order to be viable. They also lack resistance to local pests and diseases, thus necessitating the use of agrochemicals rather than leading to their reduction or elimination. Lastly, although the developed world is not so dependent upon a single crop as were the Irish on potatoes in the last century, when virulent pests or diseases arise which our current plant protection measures fail to control, as has happened, for example, with viral diseases of maize, the situation can be grave. The lack of genetic diversity in our major crop species offers little resistance to rapid spread of disease and consequent yield losses can be very serious, at least locally. To summarize, if transgenic crops come to dominate the market, will this lead to even greater losses of genetic diversity, increased use of agrochemicals and greater risks of catastrophic losses due to uncontrollable pests and diseases?

It is an unfortunate fact of life that good ideas do not always speak for themselves. They have to be simplified, packaged and promoted if they are to be heard at all and this is now as true of science as it is of any other sphere of human activity. The current style of scientific communication rarely follows the advice of Frederick Gowland Hopkins that a biochemist '... should be bold in his experiments, but cautious in his claims'. Molecular biologists certainly followed the first part of this advice to great effect and thereby transformed the way in which biological research is carried out. However the second part, although it is the path of virtue, it is not the road to recognition. Far from being cautious the claims made have been, to say the least, intemperate. So successful has been the promotion of the power of molecular genetics and the concept that everything in biology is ultimately genetically determined that almost any claim made by a high priest of molecular biology is likely to be accepted without question, though perhaps not without trepidation. Whether or not it is justified, the public is apprehensive about what they perceive as the almost limitless potential of molecular biology to

influence their lives in ways that they can neither fully understand nor control. There is also the widespread perception that large-scale, intensive agriculture serves its own ends and is immune to public opinion or consumer pressure. This ensures that any claims made for the environmental or other benefits of transgenic crops

will receive close and highly sceptical public scrutiny. To claim that the introduction of transgenic crops could herald the elimination of chemical plant protection is, in the opinion of this author, a promise that cannot be fulfilled.